VCS Oncology-Pathology Working Group
Mast Cell Tumor Subgroup
Consensus on Grading Canine Cutaneous MCTs

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Summary:
Based on critical review of the literature listed below, the Canine Cutaneous Mast Cell Tumor Subgroup has concluded and recommends the following regarding grading for canine cutaneous mast cell tumors.

Conclusions:

1. The Patnaik system has been the 'gold' standard and has provided a strong foundation in the grading of canine cutaneous mast cell tumors. However, as certain criteria within the grading system are unclear and require subjective interpretation, significant uncertainty and inter-pathologist variability exists. This has presented challenges for clinicians in determining clinical behavior from tumor grade and thus the need for adjuvant therapy, especially for "grade II" mast cell tumors (see point #4).

2. The Kiupel 2-tier system has merit; however, it also contains poorly defined, subjective criteria ("bizarre" nuclei, karyomegaly), which may continue to create inter-pathologist variability similar to that which has plagued the Patnaik scheme. From a clinical perspective, the 2-tier system may make clinical decisions similarly challenging for "low grade" mast cell tumors as those faced for Patnaik "Grade II" mast cell tumors. Additionally, with almost no therapeutic literature predicated on this grading scheme to date, it is difficult to relate low vs. high grade to chemotherapy or radiation therapy findings in past studies. Further investigation is needed to validate the 2-tier system. Until such studies are done, it is premature to adopt the Kiupel 2-tier system as the sole standard reporting mechanism for canine cutaneous mast cell tumors.

3. Mitotic Index (MI) has significant prognostic value and is a more objective variable which mitigates inter-observer variability and has been validated with two studies.[2,4] However, the prognostic cut-offs for MI vary between the studies and MI must be standardized as to the fields selected for counting and method of reporting.

4. Regardless of the grading system used, grade must be considered as only one prognostic factor and used in conjunction with the overall clinical picture: size and possibly site of the MCT, presence of metastases (stage), completeness and quality of surgical margins, prognostic markers, and new/emerging markers that have not yet been evaluated.

Recommendations and future direction:

1. Until additional studies are done to validate the 2-tier system, both the Patnaik system and the Kiupel 2-tier system should be reported for all canine cutaneous mast cell tumors. All diagnostic pathologists reporting on canine cutaneous MCTs should have the criteria for each respective system (as published)[1,5] listed and readily available/accessible for reference at the time of grading.[3,6] (See Appendix p. 4)

2. Mitotic Index should be reported in all cases and should be standardized as an absolute number: #MF/10 HPF (400X). Additionally, in adherence with evaluation methods used in both studies that demonstrated prognostic significance of MI, mitotic figures (MFs) should be counted in regions with the highest mitotic activity as determined initially on a low power scan of the specimen.

3. Further investigation into the value of prognostic markers (i.e. KIT, *c-kit* mutation, Ki67, AgNors, others still to be determined) as an adjunct to routine histopathology reporting of mast cell tumors is warranted.

Literature Reviewed:

1. Canine Cutaneous Mast Cell Tumor: Morphologic Grading and Survival Time in 83 Dogs. A. K. Patnaik, W. J. Ehler and E. G. MacEwen *Vet Pathol* 1984 21: 469.

2. Variation among pathologists in histologic grading of canine cutaneous mast cell tumors. Nicole C. Northrup1, Barry G. Harmon, Tracy L. Gieger, Cathy A. Brown, K. Paige Carmichael, Anapatricia Garcia, Kenneth S. Latimer, John S. Munday, Pauline M. Rakich, Lauren J. Richey,Nancy L. Stedman, An-Lin Cheng, Elizabeth W. Howerth. *J Vet Diagn Invest* 2005 17:245–248.

3. Variation among pathologists in the histologic grading of canine cutaneous mast cell tumors with uniform use of a single grading reference. N. C. Northrup, E. W. Howerth, B. G. Harmon, C. A. Brown, K. P. Carmicheal, A. P. Garcia, K. S. Latimer, J. S. Munday, P. M. Rakich, L. J. Richey, N. L. Stedman, T. L. Gieger. *J Vet Diagn Invest* 2005 17:561–564.

4. Mitotic Index Is Predictive for Survival for Canine Cutaneous Mast Cell Tumors. E. M. Romansik, C. M. Reilly, P. H. Kass, P. F. Moore and C. A. London. *Vet Pathol* 2007 44: 335.

5. Letter to the Editor: The Importance of the Mitotic Index as a Prognostic Factor for Survival of Canine. Cutaneous Mast Cell Tumors: A Validation Study. Lilian B. Elston, Felipe A.R. Sueiro, Josemara N. Cavalcanti and Konradin Metze. *Vet Pathol* 2009 46: 362.

6. Proposal of a 2-Tier Histologic Grading System for Canine Cutaneous Mast Cell Tumors to More Accurately Predict Biological Behavior. M. Kiupel, J. D. Webster, K. L. Bailey, S. Best, J. DeLay, C. J. Detrisac, S. D. Fitzgerald, D. Gamble, P. E. Ginn, M. H Goldschmidt, M. J. Hendrick, E. W. Howerth, E. B. Janovitz, I. Langohr, S. D. Lenz, T. P. Lipscomb, M. A. Miller, W. Misdorp, S. Moroff, T. P. Mullaney, I. Neyens, D. O'Toole, J. Ramos-Vara, T. J. Scase, F. Y. Schulman, D. Sledge, R. C. Smedley, K. Smith, P. W. Snyder, E. Southorn, N. L. Stedman, B. A. Steficek, P. C. Stromberg, V. E. Valli, S. E. Weisbrode, J. Yager, J. Heller and R. Miller. *Vet Pathol* 2011 48: 147.

Canine Cutaneous Mast Cell Tumor Grading Systems

Patnaik Grading Criteria, 1984

Table 1. Summary of the Patnaik morphologic grading classifications for canine cutaneous mast cell tumors.[8]

	Tumor grade		
	I	II	III
Location	Dermis and interfollicular spaces	Infiltrate lower dermal and subcutaneous tissue; some extend to skeletal muscles or surrounding tissues	Replace subcutaneous and deep tissues
Cell morphology	Round, monomorphic, ample distinct cytoplasm with medium-sized granules	Round to ovoid, moderately pleomorphic, with scattered spindle and giant cells; most cells distinct cytoplasm with fine granules, but some with indistinct cytoplasm and large/hyperchromatic granules	Round, ovoid, or spindle shaped, pelomorphic, medium sized; cytoplasm indistinct with granules that are fine or not obvious; many giant cells and scattered multinucleated cells
Nuclear morphology	Round, condensed chromatin	Round to indented with scattered chromatin and single nucleoli; some with double nuclei	Indented to round vesiculated, with 1 or more prominent nucleoli; common binucleated cells
Architecture, cellularity, stromal reaction	Arranged in rows or small groups, separated by mature collagen fibers of the dermis	Moderately to highly cellular, arranged in groups with thin, fibrosvascular stroma (sometimes thick and fibrocollagenous with areas of hyalinization)	Cellular, arranged in closely packed sheets; stroma fibrovascular or thick and fibrocollagenous with areas of hyalinization
Mitotic figures	None	Rare (0–2/high-power field)	Common (3–6/high-power field)
Edema and necrosis	Minimal	Areas of diffuse edema and necrosis	Edema, hemorrhage, and necrosis common

Two-Tier Grading Criteria, 2011

High-grade MCT is characterized by any one following criteria:

1. ≥ 7 MFs/10hpf
   - Evaluated in regions with highest mitotic activity
2. ≥ 3 multinucleated cells / 10hpfs
   - Where ≥ 3 nuclei constitutes a multinucleated cell
3. ≥ 3 bizarre nuclei / 10hpf
   - Highly atypical with marked indentations, segmentation, and irregular shape
4. Karyomegaly
   - Where at least 10% of neoplastic cells vary by 2-fold

References:

N. C. Northrup, T. L. Gieger. et. al. (2005). "Variation among pathologists in the histologic grading of canine cutaneous mast cell tumors with uniform use of a single grading reference." J Vet Diagn Invest 17:561–564.

Patnaik, A. K., W. J. Ehler, et al. (1984). "Canine cutaneous mast cell tumor: morphologic grading and survival time in 83 dogs." Vet Pathol 21(5): 469-474.

Kiupel, M., J. D. Webster, et al. (2011). "Proposal of a 2-tier histologic grading system for canine cutaneous mast cell tumors to more accurately predict biological behavior." Vet Pathol 48(1): 147-155.